CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074840**

Trade Name : ETODOLAC CAPSULES 200MG AND 300MG

Generic Name: Etodolac Capsules 200mg and 300mg

Sponsor : Geneva Pharmaceuticals, Inc.

Approval Date: August 29 , 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074840

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074840

APPROVAL LETTERS

ANDA 74-840

AUG 2 9 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brennan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Capsules, 200 mg and 300 mg.

Reference is also made to your amendments dated November 1, 1996; May 23, June 3, July 11, August 18, and August 28, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Capsules, 200 mg and 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lodine® Capsules, 200 mg and 300 mg, respectively, of Wyeth-Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

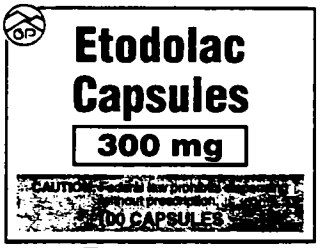
8/25/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074840

FINAL PRINTED LABELING

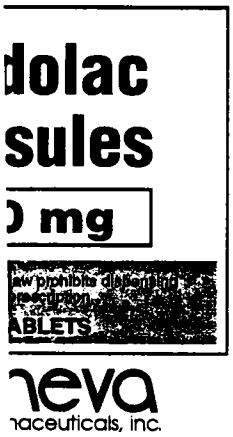


N 3 0781-2013-01 4

Each capsule contains: Etodolac 300 mg
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
ISS 95-12M Manufactured By N96/7
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP:

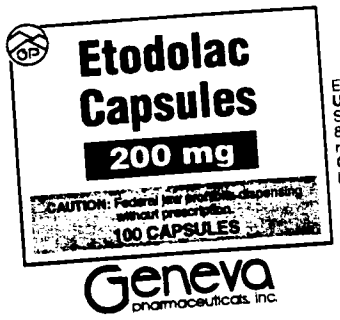


N 3 0781-2013-05 2

Each capsule contains:
Etodolac 300 mg
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
ISS 95-12M N96/7
Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:



N 3 0781-2012-01 7

200 mg

Each capsule contains: Etodolac

Usual Dosage: See package insert.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

N96/7

ISS 95-12M

Manufactured By
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

LOT:

EXP.:

2 0 1997

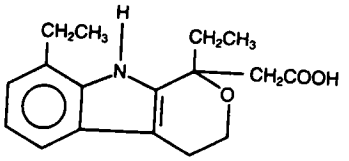
7181

ETODOLAC CAPSULES

7181-3

AUG 29 1997

DESCRIPTION: Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is:



$C_{17}H_{21}NO_3$ M.W. 287.37

It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Each capsule, for oral administration, contains 200 mg or 300 mg of etodolac. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, lactose (monohydrate), microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, sodium stearyl fumarate, starch (corn), and talc. The capsule shells and imprinting inks contain: FD & C Blue #1 Aluminum Lake, FD & C Blue #2 Aluminum Lake, FD & C Red #40 Aluminum Lake, FD & C Yellow #6 Aluminum Lake, gelatin, lecithin, pharmaceutical glaze, silicon dioxide, simethicone, sodium lauryl sulfate, titanium dioxide and ethylene glycol monoethyl ether. The **200 mg** capsule shells and imprinting inks also contain: D & C Yellow #10 Aluminum Lake, propylene glycol, and synthetic black iron oxide.

CLINICAL PHARMACOLOGY:

Pharmacology: Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac is a racemic mixture of [-] R- and [+] S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+] S-form is biologically active. Both enantiomers are stable and there is no [-] R to [+] S conversion *in vivo*.

Pharmacodynamics: Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see Clinical Trials).

Pharmacokinetics: The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption: Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 µg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1
Etodolac Steady-State Pharmacokinetic Parameters (N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability)[F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2}$, α]	0.71 ± 0.50 h
Terminal half-life [$t_{1/2}$, β]	7.3 ± 4.0 h

Antacid Effects: The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects: The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Distribution: Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

Metabolism: Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The inter-subject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

Protein Binding: Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Elimination: The mean plasma clearance of etodolac, following oral dosing is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

–etodolac, unchanged	1%
–etodolac glucuronide	13%
–hydroxylated metabolites (6-, 7- and 8-OH)	5%

(N=20)

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–etodolac, unchanged	1%
–etodolac glucuronide	13%
–hydroxylated metabolites (6-, 7-, and 8-OH)	5%
–hydroxylated metabolite glucuronides	20%
–unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.
Special Populations:
Elderly Patients: In clinical studies, etodolac clearance was reduced by about 15% in older patients (> 65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see PRECAUTIONS: Geriatric Population), as they may be more sensitive to antiprostaglandin effects than younger patients (see PRECAUTIONS: Geriatric Population).
Renal Impairment: Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.
Hepatic Impairment: In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.
Clinical Trials:
Analgesia: Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.
Osteoarthritis: The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.
INDICATIONS AND USAGE: Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.
CONTRAINDICATIONS: Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see WARNINGS: Anaphylactoid Reactions).
WARNINGS: Risk of Gastrointestinal (GI) Ulceration, Bleeding, and Perforation with Nonsteroidal, Anti-Inflammatory Drug (NSAID) Therapy: Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.
Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS: Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.
Advanced Renal Disease: In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see PRECAUTIONS: Renal Effects).
Pregnancy: In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS: Teratogenic Effects: Pregnancy Category C).
PRECAUTIONS:
General Precautions:
Renal Effects: As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.
A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.
Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients

tion, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

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Pregnancy: In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS: Teratogenic Effects: Pregnancy Category C).

PRECAUTIONS:

General Precautions:

Renal Effects: As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

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Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), etodolac should be discontinued.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma: About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients: Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal, Anti-Inflammatory (NSAID) Therapy).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see WARNINGS).

Laboratory Tests: Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

Drug Interactions:

Antacids: The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

(See Reverse)

Aspirin: When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

Warfarin: Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Cyclosporine, Digoxin, Lithium, Methotrexate: Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Phenylbutazone: Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

Drug/Laboratory Test Interactions: The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 µg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C: In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

Labor and Delivery: In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

Nursing Mothers: It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Population: As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

ADVERSE REACTIONS: Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).

Incidence Greater Than or Equal to 1%: Probably Causally Related:

Body as a whole: Chills and fever.

Digestive system: Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

Nervous system: Asthenia/malaise*, dizziness*, depression, nervousness.

Skin and appendages: Pruritus, rash.

Special senses: Blurred vision, tinnitus.

Urogenital system: Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked.

Incidence Less Than 1%: Probably Causally Related (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized):

Body as a whole: Allergic reaction, anaphylactoid reaction.

Cardiovascular system: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system: Thirst, dry mouth, *ulcerative stomatitis*, anorexia, eructation, *elevated liver enzymes, cholestatic hepatitis, hepatitis, cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis*, peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

Hemic and lymphatic system: Ecchymosis, *anemia*, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and nutritional: Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous system: Insomnia, somnolence.

Respiratory system: Asthma.

Skin and appendages: Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome*, hyperpigmentation, *erythema multiforme.*

Special senses: Photophobia, transient visual disturbances.

Urogenital system: Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.

Incidence Less Than 1%: Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians):

Body as a whole: Infection, headache.

Cardiovascular system: Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive system: Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional: Change in weight.

Nervous system: Paresthesia, confusion.

Respiratory system: Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages: Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses: Conjunctivitis, deafness, taste perversion.

Urogenital system: Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

OVERDOSAGE: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care follow-

Incidence Less Than 1%: Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians):
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Skin and appendages: Alopecia, maculopapular rash, photosensitivity, skin peeling.
Special senses: Conjunctivitis, deafness, taste perversion.
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OVERDOSAGE: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

DOSAGE AND ADMINISTRATION: As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function (see PRECAUTIONS: General Precautions: Renal Effects).

Analgesia: The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200–400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks, the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

Osteoarthritis: The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED: Etodolac capsules, for oral administration, are provided as follows:

200 mg: White capsules imprinted GG 832 with gray and black ink bands, filled with white powder in bottles of 100.

300 mg: White capsules imprinted GG 833 in gray ink, filled with white powder in bottles of 30, 100 and 500.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

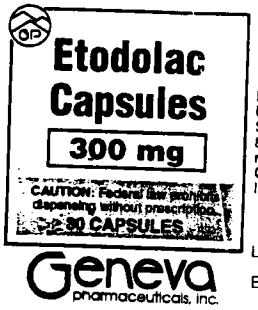
Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-5M
7181-3

C97/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020



N 3 0781-2013-31 1

Each capsule contains: Etodolac 300 mg

Usual Dosage: See package insert.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

ISS 95-12M Manufactured By N96.7
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

LOT:

EXP.:

AUG 29 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074840

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.: 3

2. ANDA # 74-840

3. NAME AND ADDRESS OF APPLICANT

Geneva Pharmaceuticals, Inc.
Attention: Beth Brennan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

4. LEGAL BASIS FOR ANDA SUBMISSION:

Approved listed drug, Lodine® Capsules containing 200 mg and 300 mg of Etodolac. Exclusivity for a new indication is granted until June 28, 1999.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Etodolac

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

January 31, 1996: Date of submission
May 23, 1997: Amendment
June 3, 1997: Amendment
The amendments are the subject of this review.

10. PHARMACOLOGICAL CATEGORY

Analgesic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsules

14. POTENCY
200 mg and 300 mg

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS : Approvable
CMC Section of the ANDA is adequate.

19. REVIEWER:
Dave Gill

DATE COMPLETED:
June 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074840

BIOEQUIVALENCE REVIEW(S)

ANDA 74-840

MAY 24 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield CO 80038-0446

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on January 31, 1996, for Etodolac Capsules 200 mg and 300 mg.

The bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals on its etodolac capsules, 300 mg, lot #6495067, comparing it to the reference product Lodine® capsules, 300 mg, lot #3941207, manufactured by Wyeth-Ayerst Laboratories has been found unacceptable to the Division of Bioequivalence due to the following reasons:

> The 90% confidence intervals for log transformed C_{max} are 77.58% to 91.31%. The Office of Generic Drugs requires that 90% confidence intervals for log transformed AUC and C_{max} data are within 80% to 125%.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

for

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

MAY 20 1996

Etodolac
200 mg, 300 mg Capsules
ANDA #74-840
Reviewer: Kuldeep R. Dhariwal
Filename: 74840SDW.196

Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446
Submission Date:
January 31, 1996

Review of Fasting and Food Studies, Dissolution Data, and Waiver Request

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting and fed conditions and dissolution data comparing its etodolac capsules, 300 mg with Wyeth-Ayerst's Lodine® capsules, 300 mg. The firm has also requested waiver of *in vivo* bioequivalence study requirements for its 200 mg capsules. To support the request, the firm has submitted comparative dissolution profiles on 200 mg capsule of its product and reference listed drug Lodine®.

Introduction:

Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. Etodolac is a nonsteroidal antiinflammatory drug with antiinflammatory, analgesic, and antipyretic properties. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion *in vivo*. Etodolac is well absorbed with a relative bioavailability of 100% when 200 mg capsules were compared with a solution. The systemic availability is at least 80% and etodolac does not undergo significant first-pass metabolism following oral administration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. Mean (± 1 SD) peak plasma concentrations range from approximately 14±4 to 37±9 ug/mL after 200 to 600 mg single doses and are reached in 80±30 minutes. The mean plasma clearance of etodolac is 47 (±16) mL/h/kg, and terminal disposition half-life is 7.3 (±4.0) hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal, but the C_{max} is reduced by 50% and T_{max} increased by 1.4-3.8 hours.

Etodolac is currently marketed as Lodine® manufactured by Wyeth-Ayerst and is available as 200 and 300 mg capsules and 400 mg tablets. Lodine® is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis, and also for the management of pain. The recommended dose for acute pain is 200-400 mg every 6-8 hours as needed, not to exceed a total daily dose of 20 mg/kg body weight. The recommended dose for osteoarthritis is initially 800 to 1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses. The total daily dose of Lodine® should not exceed 1200 mg. For patients weighing 60 kg or less, the total daily dose should not exceed 20 mg/kg.

Bioavailability of Etodolac Capsules, 300 mg under Fasting Conditions:

A. Objective:

To compare the bioavailability of Geneva's formulation of etodolac 300 mg capsules to that of a marketed reference formulation, Lodine®, 300 mg capsule, manufactured by Wyeth-Ayerst Laboratories.

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investig
Project Director
Protocol # 10856 "Bioavailability of Etodolac Capsules, 300 mg" was approved by the Institutional Review Board

Consent Form: A copy of volunteer informed consent form used in the study is given on page 86, vol. 1.1.
Study Dates: Phase I August 25-27, 1995
Phase II September 1-3, 1995
Analysis Dates: September 8-15, 1995

C. Study Design:

The study was designed as a randomized, single oral dose, two-treatment, two-period, cross-over study, with a one week wash-out period. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours postdose each period. The subjects were instructed to return to the facility for the 36 hour blood sample collection. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Phase I	Phase II
1	2,3,6,8,9,11,13,15,17,19,22,24,25	A	B
2	1,4,5,7,10,12,14,16,18,20,21,23,26	B	A

Subject numbers 12 and 23 did not complete the study.

A = Etodolac Capsules, 300 mg; Geneva Pharmaceuticals, Inc.; Lot #6495067; Batch size: Theoretical yield: Actual yield: Manufacture Date: 7/24/95; Assay: 100.6%; Content Uniformity: 98.0%
B = Etodolac Capsules, 300 mg; Wyeth Ayerst Laboratories; Lot #3941207; Assay: 99.9%; Content Uniformity: 99.6%; Expiration Date: September 1997

The subjects fasted for no fewer than 10 hours prior to dosing and 5 hours after administration of study drug. Water was restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. Identical meals were served during both phases. Blood pressure and pulse measurements were obtained predose, 4 and 24 hours postdose. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period II.

D. Subject selection:

Twenty-six healthy male subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from the study based on the following criteria:

- history of asthma, nasal polyps, esophagitis, peptic and duodenal ulcer, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in

- known allergy to etodolac or related drugs

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with heparin at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours. The plasma was transferred to prelabeled tubes and promptly frozen at -20°C. The samples were transferred to analytical laboratory on September 5, 1995.

F. Analytical Methods:

G. Pharmacokinetics/Statistics:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to five concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-six subjects entered the study. Subject #12 voluntarily withdrew after completing period I. Subject #23 tested positive on the drug screen at entry of period II and was withdrawn from the study. Twenty-four subjects completed the study.

Adverse events:

Following nine subjects experienced adverse events during the study. All events were mild in nature and resolved spontaneously.

Subject #	Phase	Product	Sign/Symptom
1	I*	Ref	Nasal stuffiness
3	I	Test	Hematoma
4	I	Ref	Lightheadedness
8	I	Test	Decreased diastolic blood pressure Faintness, nausea, fatigue
10	I	Ref	Incontinence during sleep Left thumb numbness
17	I	Test	Intermittent mild abdominal pain
18	I*	Ref	Bitter taste in mouth, diarrhea, Multiple sore muscles
20	I	Ref	Nasal congestion, tachycardia
	II	Test	Increased diastolic blood pressure
24	I	Test	Bradycardia

* reported at entry of phase II

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
3	positive yeast/HPF in urine
6	+ve blood, calcium oxalate crystals in urine high RBC/HPF in urine
11	+ve protein and hyaline castsals in urine
12	+ve leukocyte esterase & high WBC/HPF in urine
16	+ve amorphous phosphates in urine
18	high phosphorus
20	high white blood cell count
22	high white blood cell count

Deviations in the study:

There were no sampling deviations. Five subjects (#4,18,21,22, and 24) reported consuming alcohol during the interphase period. In all cases, consumption of alcohol occurred at least 24 hours prior to drug administration.

Reassays:

2. Analytical:

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of etodolac at each time point after test and reference products are shown in Table 1. There were statistically significant differences (α=0.05) in mean concentrations at 1 and 1.33 hours after dosing. The time courses of etodolac concentration after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table 2. There were significant differences between the formulations for AUC_{0-inf}, $LNAUC_{0-inf}$, C_{max}, LNC_{max}, T_{max}, and half-life. Based on least squares means, the AUC_{0-t} and AUC_{0-inf} of the test formulation were 4% and 6% lower than the respective means for the reference formulation. The test C_{max} value was 15% lower than that of the reference and occurred 29 minutes later.

The individual mean test/reference ratio for AUC_{0-t} ranged from (mean 0.967), AUC_{0-inf} ranged from (mean 0.956), and for C_{max} ranged from with a mean of 0.866.

The AUC_{0-t}/AUC_{0-inf} ratios range from 0.84-0.99 for test and 0.76-0.99 for reference product.

Following are the 90% confidence intervals provided by the firm:

Parameter	90% Confidence Interval
$LNAUC_{0-t}$	91.8-99.84%
$LNAUC_{0-inf}$	90.6-98.76%
LNC_{max}	77.58-91.31%

The 90% confidence intervals for log transformed AUC_{0-t} and AUC_{0-inf} are within the acceptable limits of 80-125%. However, 90% confidence intervals for log transformed C_{max} are outside the 80-125% limit.

Bioavailability of Etodolac Capsules, 300 mg: Food Study

A. Objective: (1) To compare the etodolac plasma levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal
(2) To compare the etodolac plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investic
Project Director:
Protocol #10857 "Bioavailability of Etodolac Capsules, 300 mg: Effect of Food Study" was approved by the National Institutional Review Board
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 88, vol. 1.4.
Study Dates: Period I August 31- September 2, 1995
Period II September 7-9, 1995
Period III September 14-16, 1995
Analysis Dates: September 19 to September 26, 1995

C. Study Design:

The protocol was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at

least 24 hours after drug administration. Subjects returned to the facility for 36 hour blood draw. The subjects (who completed the study) were assigned as follows:

Subject number	Period I	Period II	Period III
2,10,18	C	A	B
3,7,	B	A	C
5,9,16	B	C	A
4,12,17	A	B	C
6,8,13,	A	C	B
1,11,14	C	B	A

A = Etodolac Capsules, 300 mg following a standard meal; Geneva Pharmaceuticals, Inc.; Lot #6495067; Batch size: Theoretical yield: Actual yield: Manufacture Date: 7/24/95; Assay: 100.6%; Content Uniformity: 98.0%
B = Etodolac Capsules, 300 mg following a standard meal; Wyeth Ayerst Laboratories; Lot #3941207; Assay: 99.9%; Content Uniformity: 99.6%
C = Etodolac Capsules, 300 mg following an overnight fast; Geneva Pharmaceuticals, Inc.; Lot #6495067

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen healthy subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from the study based on the following criteria:

- history of asthma, nasal polyps, esophagitis, peptic and duodenal ulcer, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse

- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to etodolac or other NSAID

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol administration for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- a curfew of 12 a.m. for the nights prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity during the in-house portion of the study

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 35 minutes prior to dosing and subjects ate the entire meal within 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with heparin anticoagulant at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours. The samples were transferred to the analytical laboratory on September 18, 1995.

G. Analytical Methods:

G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to six concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Eighteen subjects were enrolled in the study. Seventeen subjects completed the study. Subject #15 voluntarily withdrew after completing phases I and II of the study. Vital signs were measured at 0 (predose), 4 and 24 hours post-dose.

Adverse events:

Three subjects reported three adverse events:

Subj. #	Period	Product	Sign/Symptom
3	III	Test (fast)	rash on back: self administered hydrocortisone

			cream
12	I	Test (fed)	headache
15	II	Test (fed)	"Pinched Feeling" lower left quadrant abdominal region

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test Result
2	low hemoglobin, hematocrit
3	high urobilinogen, + ve amorphous phosphates/HPF
4	low RBC count, hematocrit
5	high phosphorus
8	+ ve amorphous phosphates/HPF
10	high gamma GGT and calcium, slight calcium oxalate crystals in urine
12	high triglyceride
17	low hemoglobin, hematocrit; high glucose
18	+ ve amorphous phosphates/HPF

Deviations in the study:

There were five deviations in scheduled phlebotomy time:

Subj.	Period	Product	Time point	Deviation
1	II	Ref (fed)	0.33 h	2 minutes late
2	I	Test (fast)	36 h	failed to return
3	I	Ref (fed)	36 h	failed to return
5	I	Ref (fed)	36 h	failed to return
14	I	Test (fast)	36 h	failed to return

The AUC for subject #1, period II was calculated using the actual and scheduled times, and the results revealed the difference between the two to be only 0.01%. The scheduled phlebotomy time was therefore used in the AUC calculation.

Reassays:

2. Analytical:

3. Pharmacokinetics/Statistics:

The concentration of etodolac measured at each time point after each product is summarized in Table 3. From 0.33 to 2.5 hours after dosing, and from 6 to 12 hours postdose, there were significant differences in etodolac concentrations amongst the three treatments. These significant differences were a result of lower concentrations during the first 2.5 hours and higher concentrations from 6 to 12 hours after the doses given following a meal compared to the dose administered after an overnight fast. The time courses of etodolac concentration after the three

treatments are plotted in Figure 2.

Test formulation after a meal vs. reference formulation after a meal: When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for the test formulation were both 1% lower than the respective means for reference formulation. The mean C_{max} for the test product was 7% lower than that of the reference product and occurred 15 minutes earlier (Table 4).

Test formulation after a meal vs. test formulation after a 10 hour fast: The least squares means for log transformed AUC_{0-t} and AUC_{0-inf} after the meal were both 5% lower compared to 10 hour fasting. The mean C_{max} was 32% lower and 51 minutes later in test fed compared to test fasting conditions (Table 4).

The following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (fed) vs. Reference (fed)	
AUC_{0-t}	0.99
AUC_{0-inf}	0.99
C_{max}	0.93
Test (fed) vs. Test (fasted)	
AUC_{0-t}	0.95
AUC_{0-inf}	0.95
C_{max}	0.68

Ratio of means between test and reference fed are within acceptable limits. The firm has provided following 90% confidence interval values for test (fed) vs. reference (fed):

AUC_{0-t}	95.47% to 102.50%
AUC_{0-inf}	95.17% to 102.15%
C_{max}	81.48% to 105.60%

Although not required for the food study, the 90% confidence intervals for these parameters are within the acceptable range of 80% to 125%.

In Vitro Dissolution Testing:

The dissolution testing was done using apparatus 1 (basket) at 100 rpm and 1000 mL of 0.05 M pH 7.5 phosphate buffer as medium. The drug products used in the dissolution tests were from the

same lot used in the *in vivo* bioequivalence studies. The firm is proposing a specification of not less than in 20 minutes. The test and reference products pass the dissolution tests using this criteria (Table 6).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 200 mg etodolac capsules. The comparative quantitative composition of 200 mg and 300 mg capsules is shown in Table 5. The firm has submitted the dissolution profile of its 200 mg capsule and compared it with the reference listed drug Lodine® 200 mg capsule.

Comments:

Fasting Study:

1. Twenty-six subjects entered the study. Subject #12 voluntarily withdrew after completing period I. Subject #23 tested positive on the drug screen at entry of period II and was withdrawn from the study. Twenty-four subjects completed the study. Nine subjects experienced adverse events during the study. All events were mild in nature and resolved spontaneously. Eight subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation.

2. Based on least squares means, the AUC_{0-t} and AUC_{0-inf} of the test formulation were 4% and 6% lower than the respective means for the reference formulation. The test C_{max} value was 15% lower than that of the reference and occurred 29 minutes later.

3. The 90% confidence intervals for AUC_{0-t} and AUC_{0-inf} are within the acceptable range of 80-125%. However, the 90% confidence interval values for C_{max} are outside the acceptable limits. The firm does not give any explanation as to why confidence intervals for C_{max} do not meet bioequivalence criteria. The Division of Bioequivalence requires that 90% confidence intervals for log transformed AUC and C_{max} data are within 80 to 125%.

4. The study does not demonstrate that test product is bioequivalent to reference product.

5. **Not to be released under FOI**

Food Study:

1. Eighteen subjects were enrolled in the study. Seventeen subjects completed the study. Subject #15 voluntarily withdrew after completing the I and II phases of the study. Three subjects reported three adverse events. Nine subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation.

2. When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for the test formulation were both 1% lower than the respective means for reference formulation. The mean C_{max} for the test product was 7% lower than that of the reference product and occurred 15 minutes earlier.

3. The least squares means for log transformed AUC_{0-t} and AUC_{0-inf} after the meal were both 5% lower compared to 10 hour fasting. The mean C_{max} was 32% lower and 51 minutes later in test fed compared to test fasting conditions.

4. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test fed and reference fed are within acceptable limits.

5. The food study is acceptable.

Dissolution Testing:

There is no USP method available for dissolution testing of etodolac capsules. The firm has used the method which is same as recommended by the agency. The dissolution data are acceptable.

Waiver Request:

1. The two strengths of etodolac capsules have almost identical total capsule weight (200 mg strength=522 mg; 300 mg strength=512 mg). Inactive ingredients calculated as per cent of total capsule weight are almost in identical amounts in the two strengths. The main difference is in the amount of microcrystalline cellulose and lactose which are present in higher quantities in 200 mg

capsule. These two ingredients are fillers and added in higher quantities in 200 mg capsule to compensate for the difference in the amount of active ingredient.

2. The dissolution profiles of test and reference 200 mg capsules are similar except at 5 minute time point. Both the products meet the specifications of (Q) in 20 minutes.

Deficiency:

1. The 90% confidence intervals for log transformed C_{max} are 77.58% to 91.31%. The Division of Bioequivalence requires that 90% confidence intervals for log transformed AUC and C_{max} data are within 80% to 125%.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals on its etodolac capsules, 300 mg, lot #6495067, comparing it to the reference product Lodine® capsules, 300 mg, lot #3941207, manufactured by Wyeth-Ayerst Laboratories has been found unacceptable to the Division of Bioequivalence due to the reasons given in deficiency.

2. The bioequivalence study conducted under fed conditions by Geneva Pharmaceuticals on its etodolac capsules, 300 mg, lot #6495067, comparing it to the reference product Lodine® capsules, 300 mg, lot #3941207 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Geneva's etodolac capsule, 300 mg is similar to that of the reference product Lodine® capsule, 300 mg manufactured by Wyeth-Ayerst.

3. The dissolution testing conducted by Geneva Pharmaceuticals is acceptable.

4. The waiver of *in vivo* bioequivalence study requirements for the firm's 200 mg capsules is denied pending acceptable bioequivalence fasting study.

5. From bioequivalence standpoint, the firm has not met the *in vivo* bioavailability requirements and the application is not approvable.

The firm should be informed of the recommendations and deficiency.

Table 1

Etodolac Plasma Concentrations (μg/mL) in Fasting Study: Arithmetic means ± Standard Deviation (N=24)

Time (h)	Test	Reference	Test/Ref	Signific. at p=0.05
0	0	0	-	
0.33	4.367±3.84	3.819±3.61	1.14	NS
0.67	14.39±7.87	17.11±11.15	0.84	NS
1	14.90±8.26	19.31±9.02	0.77	p=<0.05
1.33	15.14±8.48	18.69±6.49	0.81	p=<0.05
1.67	14.46±6.94	16.83±4.70	0.86	NS
2	14.63±6.25	15.31±4.85	0.96	NS
2.5	13.41±3.83	13.87±4.13	0.97	NS
3	11.86±3.48	12.57±3.59	0.94	NS
4	10.69±3.86	10.56±3.46	1.01	NS
6	6.41±2.915	6.34±2.50	1.01	NS
8	4.213±1.66	4.17±1.73	1.01	NS
10	3.755±1.61	3.71±1.58	1.01	NS
12	3.143±1.41	3.131±1.56	1.00	NS
16	2.075±1.10	2.079±1.22	1.00	NS
24	1.299±1.00	1.299±1.03	1.00	NS
36	0.470±0.49	0.545±0.67	0.86	NS
Parameter				
AUC_{0-t} (μg/mLxh)	125.2±48.5	130.1±49.9	0.96	
AUC_{0-inf} (μg/mLxh)	132.3±57.9	140.2±65.3	0.94	
C_{max} (μg/mL)	21.25±6.40	25.0±6.90	0.85	
T_{max} (h)	1.924±1.08	1.445±0.86	1.33	
Half-life (h)	8.253±2.24	8.822±3.05	0.94	
Rate constant	0.089±0.02 (h^{-1})	0.085±0.02	1.04	

Table 2

Etodolac Plasma Concentrations in the Fasting Study (N=24)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} ($\mu g/mL x h$)	125.1±2.0	130.5±2.0	0.96	92-100%
AUC_{0-inf} ($\mu g/mL x h$)	132.2±2.44	140.5±2.44	0.94	90-98%
C_{max} ($\mu g/mL$)	21.28±0.76	25.10±0.76	0.85	77-92%
T_{max} (h)	1.923±0.15	1.442±0.15	1.33	107-160%
Half-life (h)	8.266±0.18	8.844±0.18	0.93	88-99%
Rate constant (h^{-1})	0.089±0.001	0.085±0.001	1.04	100-109%
$LNAUC_{0-t}$	4.764±0.017	4.808±0.017	0.96	92-100%
$LNAUC_{0-inf}$	4.809±0.017	4.865±0.017	0.95	91-99%
LNC_{max}	3.012±0.033	3.184±0.033	0.84	78-91%

Table 3

Etodolac Plasma Concentrations (μg/mL) in the Food Study (N=17): Arithmetic Means ± Standard Deviation (SD)

Time h	Test-Fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
0	0	0	0			
0.33	0.325±0.77	0.127±0.16	2.401±2.914	2.56	0.14	0.05
0.67	2.368±4.37	1.210±1.68	10.46±7.685	1.96	0.23	0.12
1	4.514±4.61	2.965±3.57	13.83±8.436	1.52	0.33	0.21
1.33	7.653±6.04	4.656±3.89	13.84±7.524	1.64	0.55	0.34
1.67	9.539±5.64	7.305±4.83	14.32±7.696	1.31	0.67	0.51
2	10.19±4.68	8.940±4.84	14.42±7.762	1.14	0.71	0.62
2.5	10.47±2.78	10.71±4.40	13.60±5.614	0.98	0.77	0.79
3	11.24±1.99	11.88±4.60	12.23±4.159	0.95	0.92	0.97
4	12.02±3.29	12.98±3.58	11.21±2.155	0.93	1.07	1.16
6	8.524±2.22	9.618±2.75	6.915±1.483	0.89	1.23	1.39
8	5.062±1.54	5.573±1.89	4.476±1.258	0.91	1.13	1.24
10	3.836±1.36	4.102±1.46	3.562±1.178	0.94	1.08	1.15
12	2.856±0.98	3.114±1.07	2.734±0.892	0.92	1.04	1.14
16	1.921±0.99	1.831±0.75	1.770±0.652	1.05	1.09	1.03
24	1.001±0.55	0.931±0.44	0.877±0.335	1.08	1.14	1.06
36	0.324±0.26	0.323±0.25	0.314±0.176	1.00	1.03	1.03
Parameters						
AUC_{0-t} (μg/mLxh)	110.9±27.2	112.1±27.6	115.7±25.88	0.99	0.96	0.97
AUC_{0-inf} (μg/mLxh)	115.0±30.1	116.4±29.7	119.7±27.11	0.99	0.96	0.97
C_{max} (μg/mL)	14.23±4.46	14.99±2.81	21.17±7.13	0.95	0.67	0.71
T_{max} (h)	2.873±1.34	3.128±1.32	2.020±1.15	0.92	1.42	1.55
Half-life (h)	7.305±1.73	6.938±1.26	7.351±1.31	1.05	0.99	0.94
Rate constant (h^{-1})	0.098±0.02	0.103±0.02	0.097±0.02	0.96	1.02	1.06

Table 4

Etodolac Plasma Concentrations in the Food Study (N=17)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test-fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
AUC_{0-t} ($\mu g/mLxh$)	110.3±1.68	111.3±1.68	115.3±1.68	0.99	0.96	0.97
AUC_{0-inf} ($\mu g/mLxh$)	114.3±1.75	115.7±1.75	119.3±1.75	0.99	0.96	0.97
C_{max} ($\mu g/mL$)	14.23±1.04	14.95±1.04	21.18±1.04	0.95	0.67	0.71
T_{max} (h)	2.832±0.29	3.083±0.29	1.975±0.29	0.92	1.43	1.56
$LNAUC_{0-t}$ (Antiln)	4.674±0.014 (107.1)	4.685±0.014 (108.3)	4.724±0.014 (112.7)	0.99	0.95	0.96
$LNAUC_{0-inf}$ (Antiln)	4.707±0.014 (110.7)	4.721±0.014 (112.3)	4.758±0.014 (116.5)	0.99	0.95	0.96
LNC_{max} (Antiln)	2.612±0.054 (13.62)	2.687±0.054 (14.68)	2.998±0.054 (20.04)	0.93	0.68	0.73

Table 5

Comparative Quantitative Composition of Etodolac 200 mg and 300 mg Capsules

Ingredient	200 mg Capsule mg	%	300 mg Capsule mg	%
Etodolac	200	38.31	300	58.59
Microcrystalline Cellulose, NF				
Sodium Lauryl Sulfate, NF				
Lactose Monohydrate, NF				
Povidone, USP				
Purified Water, USP				
Microcrystalline Cellulose,NF				
Lactose Monohydrate,NF				
Sodium Starch Glycolate, NF				
Colloidal Silicon Dioxide, NF				
Sodium Stearyl Fumarate, NF				
Talc, USP				
#0 Opaque White Cap/Opaque White Body, Body and Cap Imprinted GG832 with Gray & Black Ink Bands				
#0 Opaque White Cap/Opaque White Body, Body and Cap Imprinted GG 833 in Gray Ink				
Corn Starch, NF				
Total Capsule Weight	522.00	99.96	512.00	99.98

Table 6 . In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsules
Dose Strength: 200 mg, 300 mg
ANDA No.: 74840
Firm: Geneva Pharmaceuticals, Inc.
Submission Date: January 31, 1996
File Name: 74840SDW.196

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM:100
No. Units Tested: 12
Medium: 0.05 M pH 7.5 Phosphate Buffer Volume: 1000 mL
Specifications: NLT (Q) in 20 minutes
Reference Drug: Lodine® Capsules (Wyeth-Ayerst)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6495098 Strength(mg) 200			Reference Product Lot # 3940627 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
5	79		19.0	66		15.6
10	98		4.2	100		5.1
15	100		1.0	103		1.4
20	101		1.3	104		1.3
30	101		1.2	104		0.9

Sampling Times (Minutes)	Test Product Lot #6495067 Strength(mg) 300			Reference Product Lot # 3941207 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
5	26		42.7	15		62.7
10	60		18.2	48		31.0
15	80		9.8	84		10.5
20	93		3.2	95		3.4
30	94		1.8	98		1.4

Figure 1: Mean Etodolac Plasma Levels Fasting Study

#005 – 30 – 10856

N = 24

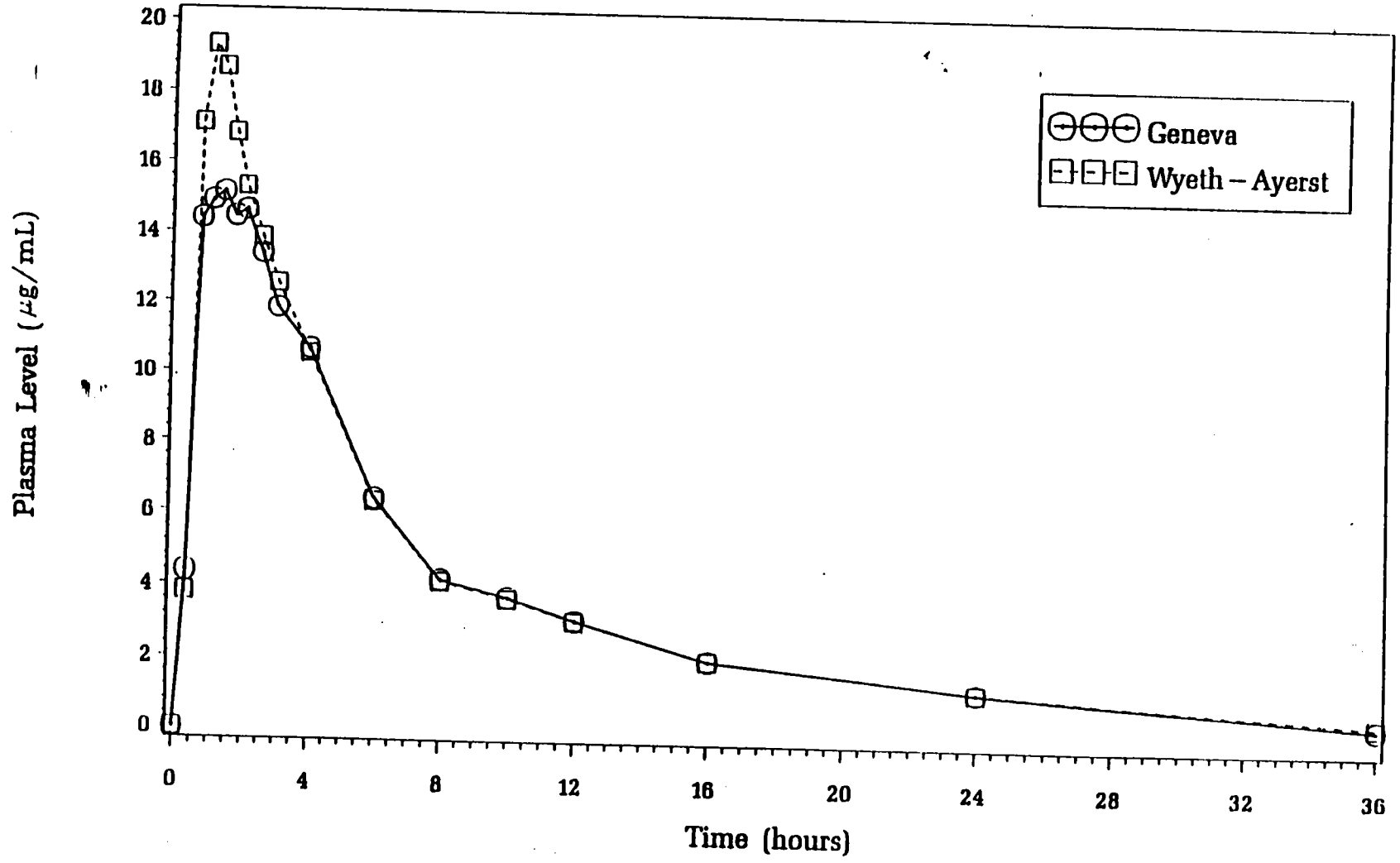


figure 1

Figure 1: Mean Etodolac Plasma Levels

#005 – 31 – 10857

N = 17

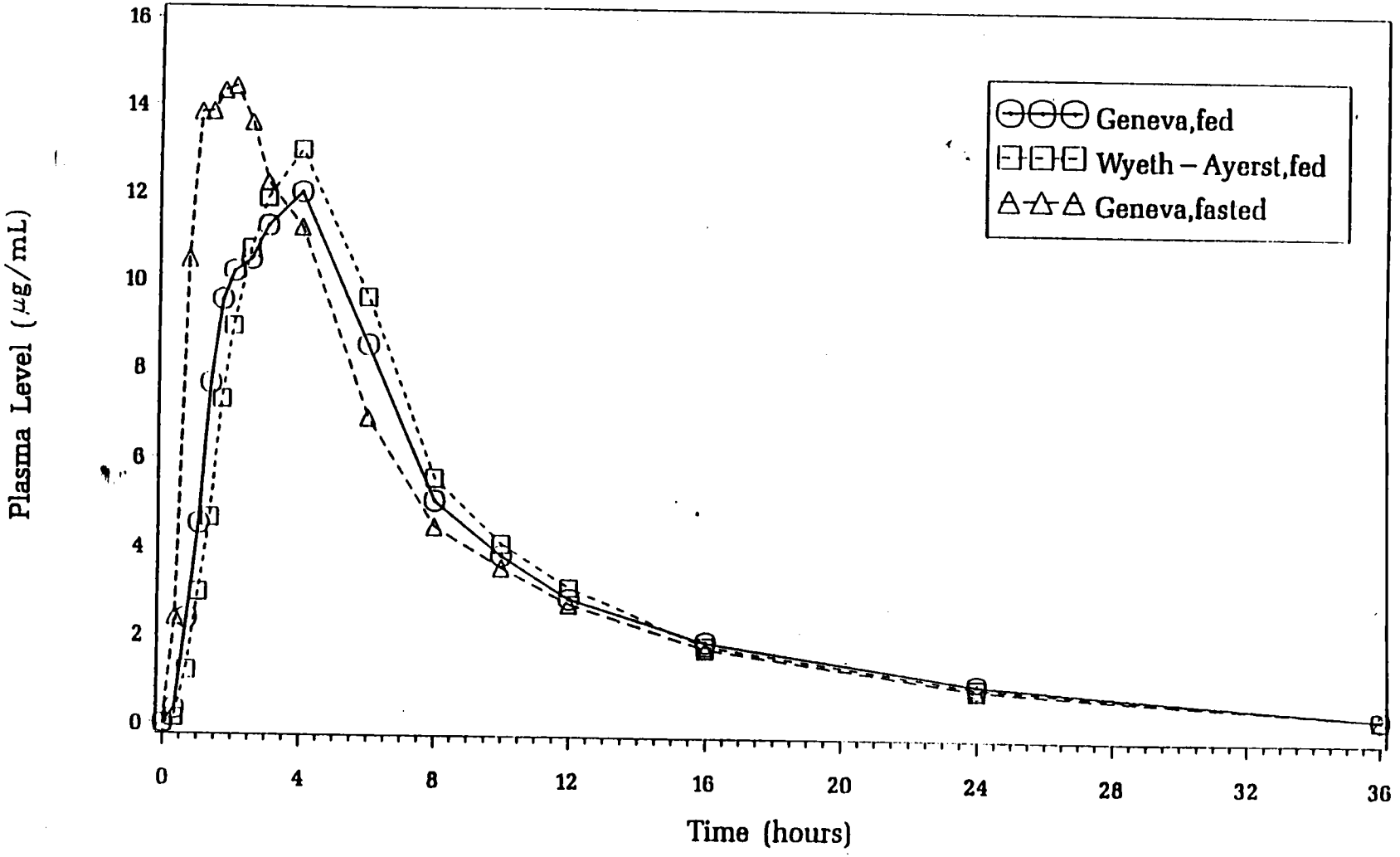


Figure 2

MAY 27 1997

Etodolac	Geneva Pharmaceuticals, Inc.
200 mg, 300 mg Capsules	2555 W. Midway Blvd.
ANDA #74-840	Broomfield, CO 80038-0446
Reviewer: Kuldeep R. Dhariwal	Submission Date:
Filename: 74840SDW.N96	November 1, 1996

Review of Fasting and Food Studies, Dissolution Data, and Waiver Request

The firm had submitted a single-dose *in vivo* bioequivalence study under fasting and fed conditions and dissolution data comparing its etodolac capsules, 300 mg with Wyeth-Ayerst's Lodine® capsules, 300 mg in January 1996. The firm had also requested waiver of *in vivo* bioequivalence study requirements for its 200 mg capsules. To support the request, the firm submitted comparative dissolution profiles on 200 mg capsule of its product and reference listed drug Lodine®. The bioequivalence study submitted under fasting conditions was not acceptable because 90% confidence intervals for log transformed C_{max} were outside acceptable 80-125% limit (77.58-91.31%). (File name: 74840SDW.196).

The firm submitted new fasting and fed studies on its 300 mg capsule and dissolution data on 200 mg and 300 mg capsules as an amendment on November 1, 1996. This is a review of the new study.

Introduction:

Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. Etodolac is a nonsteroidal antiinflammatory drug with antiinflammatory, analgesic, and antipyretic properties. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion *in vivo*. Etodolac is well absorbed with a relative bioavailability of 100% when 200 mg capsules were compared with a solution. The systemic availability is at least 80% and etodolac does not undergo significant first-pass metabolism following oral administration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. Mean (± 1 SD) peak plasma concentrations range from approximately 14±4 to 37±9 μg/mL after 200 to 600 mg single doses and are reached in 80±30 minutes. The mean plasma clearance of etodolac

is 47 (±16) mL/h/kg, and terminal disposition half-life is 7.3 (±4.0) hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal, but the C_{max} is reduced by 50% and T_{max} increased by 1.4-3.8 hours.

Etodolac is currently marketed as Lodine[R] manufactured by Wyeth-Ayerst and is available as 200 and 300 mg capsules and 400 mg tablets. Lodine[R] is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis, and also for the management of pain. The recommended dose for acute pain is 200-400 mg every 6-8 hours as needed, not to exceed a total daily dose of 20 mg/kg body weight. The recommended dose for osteoarthritis is initially 800 to 1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses. The total daily dose of Lodine[R] should not exceed 1200 mg. For patients weighing 60 kg or less, the total daily dose should not exceed 20 mg/kg.

Bioavailability of Etodolac Capsules, 300 mg under Fasting Conditions:

A. Objective:

To compare the bioavailability of Geneva's formulation of etodolac 300 mg capsules to that of a marketed reference formulation, Lodine®, 300 mg capsule, manufactured by Wyeth-Ayerst Laboratories.

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investigator:
Project Director:
Protocol # 11010 "Bioavailability of Etodolac Capsules, 300 mg" was approved by the Institutional Review Board

Consent Form: A copy of volunteer informed consent form used in the study is given on page 86, vol. 1.1.
Study Dates: Period I May 3-5, 1996
Period II May 10-12, 1996
Analysis Dates: May 31 to June 14, 1996

C. Study Design:

The study was designed as a randomized, single oral dose, two-treatment, two-period, cross-over study, with a one week wash-out

period. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours postdose each period. The subjects were instructed to return to the facility for the 36 hour blood sample collection. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Phase I	Phase II
1	1,4,5,8,9,11,14,16,17,20,21,24,25	A	B
2	2,3,6,7,10,12,13,15,18,19,22,23,26	B	A

Subject numbers 5, 11, and 14 did not complete the study.

A = Etodolac Capsules, 300 mg; Geneva Pharmaceuticals, Inc.; Lot #6496016; Lot size: Theoretical Yield , Actual Yield Manufacture Date: 4/96; Assay: 100.7%; Content Uniformity: 99.9%
B = Etodolac Capsules, 300 mg; Wyeth-Ayerst Laboratories; Lot #3941207; Assay: 101.1%; Content Uniformity: 101.1%; Expiration Date: September 1997

The subjects fasted for no fewer than 10 hours prior to dosing and 5 hours after administration of study drug. Water was restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. Identical meals were served during both phases. Blood pressure and pulse measurements were obtained predose, 4 and 24 hours postdose. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period II.

D. Subject selection:

Twenty-six healthy male subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from the study based on the following criteria:

- history of asthma, nasal polyps, esophagitis, peptic and duodenal ulcer, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to etodolac or related drugs

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with heparin at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours. The plasma was transferred to prelabeled tubes and promptly frozen at -20°C. The samples were transferred to analytical laboratory on May 16, 1996.

F. Analytical Methods:

G. Pharmacokinetics/Statistics:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to five concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-six subjects entered the study. Subject #5 and 14 did not return for period II. Subject #11 withdrew before period II dosing for personal reasons. Twenty-three subjects completed the study.

Adverse events:

One subject (#14) experienced restlessness, lightheaded and `shakes' during period I (test drug).

Deviations in the study:

There was one sampling deviation. Twenty minute sample in period I for subject #10 was withdrawn 3 minutes late. The AUC_{0-t} value calculated using actual time was almost the same as calculated using scheduled time.

Reassays:

2. Analytical:

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of etodolac at each time point after test and reference products are shown in Table 2. There were no significant (α=0.05) differences in mean concentrations between the formulations at any time after dosing. The time courses of etodolac concentrations after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Tables 2 and 3. There was almost no difference in

AUC_{0-t} and AUC_{0-inf} of the test and reference products. The C_{max} of the test product was 10% lower than that of the reference product and occurred about 2 minutes earlier.

The individual test/reference ratio for AUC_{0-t} ranged from (mean 1.016), AUC_{0-inf} ranged from (mean 1.014) and for C_{max} ranged from with a mean of 0.917 (Table 4).

The AUC_{0-t}/AUC_{0-inf} ratios range from 0.80-0.99 for test and 0.85-0.99 for reference product (Table 5).

Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	94-106%	93.99-106.37%
$LNAUC_{0-inf}$	94-106%	94.15-106.25%
LNC_{max}	83-98%	83.19-97.93%

The 90% confidence intervals are within the acceptable range of 80-125%. Statistical analysis of data show significant period effect ($p=0.0327$) for C_{max} and significant treatment effect ($p=0.0424$) for log transformed C_{max}.

The reviewer performed some calculations (3 subjects: test drug, 2 subjects: reference drug, randomly selected) to determine the accuracy of the AUC_{0-t} and AUC_{0-inf} values given in the application. The reviewer's values were same as provided by the firm.

Bioavailability of Etodolac Capsules, 300 mg: Food Study

A. Objective: (1) To compare the etodolac plasma levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal
(2) To compare the etodolac plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investiga
Project Director:
Protocol #11011 "Bioavailability of Etodolac Capsules, 300 mg: Effect of Food Study" was approved by the National Institutional Review Board
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 88, vol. B3.4.

Study Dates: Period I May 1-3, 1996
Period II May 8-10, 1996
Period III May 15-17, 1996
Analysis Dates: June 1 to 7, 1996

C. Study Design:

The protocol was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 24 hours after drug administration. Subjects returned to the facility for 36 hour blood draw. The subjects (who completed the study) were assigned as follows:

Subject number	Period I	Period II	Period III
1,9,15	C	A	B
11,18	B	A	C
3,8	B	C	A
6,	A	B	C
5,10,13	A	C	B
7,14	C	B	A

A = Etodolac Capsules, 300 mg following a standard meal; Geneva Pharmaceuticals, Inc.; Lot #6496016; Batch size:
Manufacture Date: 4/96; Assay: 100.7%; Content Uniformity: 99.9%
B = Etodolac Capsules, 300 mg following a standard meal; Wyeth-Ayerst Laboratories; Lot #3941207; Assay: 101.1%; Content Uniformity: 101.1%
C = Etodolac Capsules, 300 mg following an overnight fast; Geneva Pharmaceuticals, Inc.; Lot #6496016

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen subjects were enrolled in the study with essentially same inclusion and exclusion criteria as used for fasting study.

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 35 minutes prior to dosing and subjects ate the entire meal within 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection:

Ten milliliters of venous blood were obtained in Vacutainers with heparin anticoagulant at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours. The samples were centrifuged at 2500 rpm, 10°C for 20 minutes. The plasma was separated and stored at -20°C. The samples were transferred to the analytical laboratory on May 21, 1996.

G. Analytical Methods, Pharmacokinetics/Statistics:

Same as for fasting study.

H. Results:

1. Clinical:

Eighteen subjects were enrolled in the study. Thirteen subjects completed the study. Subject #12 and 16 did not return for period II; subject #4 did not return for period III; subject #2 voluntarily withdrew during period II for personal reasons. Subject #17 was withdrawn prior to period II dosing because of heart burn and vomiting.

Adverse events: Subject #11 experienced diarrhea on 5/14/96.

Deviations in the study:

Three subjects (#2 period I; #4 period II; and #8 period II) did not return to the clinic for 36 hour sample (Subjects 2 and 4 did not complete the study).

Subject #13 was under the influence of alcohol when returned to the clinic for 36 hour sample in period III.

Subject #6 took multivitamin during the inter-phase.

Reassays: None

2. Analytical: -

Pre-study Method Validation: same as for fasting study.

3. Pharmacokinetics/Statistics:

The concentration of etodolac measured at each time point after each product is summarized in Table 6. The time courses of etodolac concentration after the three treatments are plotted in Figure 2.

Test formulation after a meal vs. reference formulation after a meal: When the test and reference formulations were administered after a meal, the arithmetic means for AUC_{0-t} and AUC_{0-inf} for the test formulation were both 1% higher than the respective means for reference formulation. The mean C_{max} of the test formulation was 1% lower than that of the reference product and occurred 53 minutes later.

Test formulation after a meal vs. test formulation after a 10 hour fast: The arithmetic means for AUC_{0-t} and AUC_{0-inf} after the meal were both 5% lower compared to 10 hour fasting. The mean C_{max} was 39% lower and 123 minutes later in test fed compared to the test fasting conditions.

The following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (fed) vs. Reference (fed)	
AUC_{0-t}	1.01
AUC_{0-inf}	1.01
C_{max}	0.99
Test (fed) vs. Test (fasted)	
AUC_{0-t}	0.95
AUC_{0-inf}	0.95
C_{max}	0.61

Ratio of means between test and reference fed are within acceptable limits.

The reviewer performed some calculations (3 subjects: test-fed) to check the accuracy of the AUC_{0-t} and AUC_{0-inf} values given in the application. The reviewer's values were same as provided by the firm.

In Vitro Dissolution Testing: (Non-USP method)

The dissolution testing was done using apparatus 1 (basket) at 100 rpm and 1000 mL of 0.05 M pH 7.5 phosphate buffer as medium (FDA method). The drug products used in the dissolution tests were from the same lot used in the *in vivo* bioequivalence studies. The test and reference products dissolve more than in 20 minutes and meet the specifications (Table 7).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 200 mg etodolac capsules. The comparative quantitative composition of 200 mg and 300 mg capsules is shown in Table 1. The composition of the two strengths is similar. The only difference is in the amounts of microcrystalline cellulose and lactose. These ingredients are added in higher amounts in 200 mg capsule to compensate for the difference in the amount of active ingredient. The firm has submitted the dissolution profile of its 200 mg capsule and compared it with the reference listed drug Lodine® 200 mg capsule.

Comments:

Fasting Study:

1. Twenty-six subjects entered the study. Subject #11 voluntarily withdrew after completing period I. Subject #5 and 14 did not return for period II. Twenty-three subjects completed the study. One subject experienced mild adverse events during the study which required no medication.

2. There was almost no difference in AUC_{0-t} and AUC_{0-inf} of the test and reference products. The C_{max} of the test product was 10% lower than that of the reference product and occurred about 2 minutes earlier.

3. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max} are within the acceptable range of 80-125%.

4. Subject #13 had first measured value (0.33 hour) as C_{max} in period II. This reviewer repeated statistical analysis of the data after eliminating this subject. The 90% confidence intervals remained within 80-125% limit:

$LNAUC_{0-t}$	93.62-106.55%
$LNAUC_{0-inf}$	94.38-106.95%
LNC_{max}	83.83-98.99%

There was no sequence, period or treatment effect for any of the pharmacokinetic parameters after eliminating subject #13.

5. The study demonstrates that test product is bioequivalent to the reference product.

6. Differences between firm's earlier study and this study: Firm's earlier biostudy on 300 mg capsules submitted on January 31, 1996 was not acceptable because 90% CI for LNC_{max} were 77.58-91.31%. In the present study, the firm made minor quantitative changes in its formulation. The test drug is therefore from a different lot. The reference drug in the two studies is from the same lot. The study was conducted at same clinical center and samples were analyzed by same method.

Food Study:

1. Eighteen subjects were enrolled in the study. Thirteen subjects completed the study. Subject #2 voluntarily withdrew during period II. Subjects #12 and 16 did not return for period II and #4 did not return for period III. Subject #17 was withdrawn prior to period II dosing due to complaints of heart burn and vomiting.

2. When the test and reference formulations were administered after a meal, the AUC_{0-t} and AUC_{0-inf} of the test formulation were both 1% higher than the respective means for reference formulation. The mean C_{max} of the test product was 1% lower than that of the reference product and occurred 53 minutes later.

3. The test arithmetic means for AUC_{0-t} and AUC_{0-inf} after the meal were both 5% lower compared to 10 hour fasting. The mean C_{max} was 39% lower and 123 minutes later in test fed compared to the test fasting conditions.

4. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test fed and reference fed are within acceptable limits.

5. The food study is acceptable.

Dissolution Testing:

There is no USP method available for dissolution testing of etodolac capsules. The firm has used the method which is same as recommended by the agency. The test and reference capsules dissolve more than in 20 minutes. However, the % CV for both the products is very high at early time points. The dissolution data are acceptable.

Waiver Request:

1. The two strengths of etodolac capsules have same total capsule weight. Inactive ingredients calculated as per cent of total capsule weight are in identical amounts in the two strengths. The main difference is in the amounts of microcrystalline cellulose and lactose which are present in higher quantities in 200 mg capsule. These two ingredients are fillers and added in higher quantities in 200 mg capsule to compensate for the difference in the amount of active ingredient.

2. The dissolution profiles of test and reference 200 mg capsules are similar except at early time points. Both the products meet the specifications of (Q) in 20 minutes.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals on its etodolac 300 mg capsules, lot #6496016, comparing it to the reference product Lodine® 300 mg capsules, lot #3941207 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting

conditions, Geneva's etodolac 300 mg capsule is bioequivalent to the reference product Lodine® 300 mg capsule manufactured by Wyeth-Ayerst.

2. The *in vivo* bioequivalence study conducted under fed conditions by Geneva Pharmaceuticals on its etodolac 300 mg capsules, lot #6496016, comparing it to the reference product Lodine® 300 mg capsules, lot #3941207 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Geneva's etodolac 300 mg capsule is similar to that of the reference product Lodine® 300 mg capsule manufactured by Wyeth-Ayerst.

3. The dissolution testing conducted on etodolac 200 mg and 300 mg capsules is acceptable. The firm has conducted acceptable *in vivo* bioequivalence studies comparing its etodolac 300 mg capsules with the reference product Lodine® 300 mg capsules manufactured by Wyeth-Ayerst. The formulation for the 200 mg strength of the test product is proportionally similar to the 300 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 200 mg capsule is granted. The 200 mg capsule from Geneva Pharmaceuticals is therefore deemed bioequivalent to the 200 mg Lodine® capsule manufactured by Wyeth-Ayerst.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of etodolac in the dosage form is dissolved in 20 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

5/21/97

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

Date 5/21/97

Concur: _____ Date 5/27/97

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74840 (original, duplicate), Dhariwal, HFD-655 (S. Nerurkar), HFD-650 (Director), Drug File, Division File

Draft: 042597; Final: 052197

Not to be released under FOI

Table 1

Comparative Quantitative Composition of Etodolac 200 mg and 300 mg Capsules

Ingredient	200 mg Capsule mg	200 mg Capsule %	300 mg Capsule mg	300 mg Capsule %
Etodolac	200	39.06	300	58.59
Microcrystalline Cellulose, NF				
Sodium Lauryl Sulfate, NF				
Povidone, USP				
Purified Water, USP				
Lactose Monohydrate, NF				
Sodium Starch Glycolate, NF				
Colloidal Silicon Dioxide, NF				
Sodium Stearyl Fumarate, NF				
Talc, USP				
#0 Opaque White Cap/Opaque White Body, Body and Cap Imprinted GG832 with Gray & Black Ink Bands				
#0 Opaque White Cap/Opaque White Body, Body and Cap Imprinted GG 833 with Gray Ink Bands				
Corn Starch, NF				
Total Capsule Weight	512.00	99.96	512.00	99.97

Table 2

Etodolac Plasma Concentrations (μg/mL) and Pharmacokinetic Parameters in Fasting Study: Arithmetic means ± Standard Deviation (N=23)

Time (h)	Test	Reference	Test/Ref Ratio	Signific. at p=0.05
0	0	0	-	
0.33	6.041±6.616	5.006±5.530	1.21	NS
0.67	18.02±9.487	17.64±11.64	1.02	NS
1	19.77±8:151	19.62±10.64	1.01	NS
1.33	19.35±6.934	18.68±9.386	1.04	NS
1.67	18.11±6.222	18.34±6.285	0.99	NS
2	16.87±5.506	18.57±5.449	0.91	NS
2.5	15.42±4.006	17.12±6.328	0.90	NS
3	13.79±3.451	15.18±5.268	0.91	NS
4	11.99±3.180	12.28±3.688	0.98	NS
6	6.850±1.754	6.749±1.812	1.01	NS
8	4.738±1.454	4.583±1.414	1.03	NS
10	4.245±1.370	4.217±1.342	1.01	NS
12	3.644±1.256	3.513±1.236	1.04	NS
16	2.322±1.009	2.285±0.999	1.02	NS
24	1.455±0.878	1.344±0.710	1.08	NS
36*	0.466±0.459	0.502±0.497	0.93	NS
Parameter				
AUC_{0-t} (μg/mLxh)	143.6±37.50	143.9±40.57	1.00	
AUC_{0-inf} (μg/mLxh)	151.0±45.91	151.5±49.21	1.00	
C_{max} (μg/mL)	25.35±6.542	28.28±7.094	0.90	
T_{max} (h)	1.392±0.884	1.435±0.798	0.97	
Half-life (h)	8.187±2.494	8.121±2.264	1.01	
Elim. rate constant (h^{-1})	0.0901±0.02	0.0903±0.02	1.00	

* N=22

Table 3

Etodolac Plasma Concentrations in the Fasting Study (N=23)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} ($\mu g/mLxh$)	142.9±3.61	143.2±3.61	1.00	94-106%
AUC_{0-inf} ($\mu g/mLxh$)	150.1±3.63	150.5±3.64	1.00	94-106%
C_{max} ($\mu g/mL$)	25.48±0.93	28.01±0.93	0.91	83-99%
T_{max} (h)	1.389±0.16	1.470±0.16	0.95	67-122%
Half-life (h)	8.115±0.32	8.045±0.32	1.01	91-110%
Elim. rate constant (h^{-1})	0.091±0.002	0.091±0.002	1.00	93-106%
$LNAUC_{0-t}$ (Antiln)	4.9321±0.025 138.7	4.9321±0.025 138.7	1.00	94-106%
$LNAUC_{0-inf}$ (Antiln)	4.9748±0.025 144.7	4.9746±0.025 144.7	1.00	94-106%
LNC_{max} (Antiln)	3.2010±0.033 24.56	3.3034±0.033 27.21	0.90	83-98%

Table 4

Test/Reference Ratio for Pharmacokinetic Parameters in Individual Subjects (Fasting Study)

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1			
2	2			
3	2			
4	1			
6	2			
7	2			
8	1			
9	1			
10	2			
12	2			
13	2			
15	2			
16	1			
17	1			
18	2			
19	2			
20	1			
21	1			
22	2			
23	2			
24	1			
25	1			
26	2			
Mean		1.016	1.014	0.917
Range				

Table 5

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects (Fasting Study)

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1	0.97	0.96
2	0.93	0.95
3	0.96	0.97
4	0.96	0.96
6	0.98	0.97
7	0.96	0.97
8	0.97	0.97
9	0.99	0.99
10	0.98	0.94
12	0.96	0.97
13	0.98	0.85
15	0.98	0.99
16	0.97	0.97
17	0.87	0.94
18	0.80	0.87
19	0.97	0.98
20	0.98	0.98
21	0.99	0.99
22	0.98	0.98
23	0.99	0.93
24	0.99	0.99
25	0.94	0.95
26	0.95	0.96

Table 6

Etodolac Plasma Concentrations (μg/mL) in the Food Study (N=13): Arithmetic Means ± Standard Deviation

Time h	Test-Fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
0	0	0	0			
0.33	0.0245±0.06	0.9146±2.97	1.602±2.225	0.03	0.02	0.57
0.67	1.540±3.870	1.620±3.376	15.90±9.331	0.95	0.10	0.10
1	2.853±4.282	3.271±4.499	20.83±9.952	0.87	0.14	0.16
1.33	5.086±5.781	5.604±5.329	19.16±8.019	0.91	0.27	0.29
1.67	7.224±6.116	8.482±4.756	17.36±5.476	0.85	0.42	0.49
2	8.487±5.300	11.09±5.143	17.26±5.226	0.77	0.49	0.64
2.5	10.52±3.189	13.17±3.921	14.84±3.523	0.80	0.71	0.89
3	12.02±3.234	13.00±2.886	12.62±2.720	0.92	0.95	1.03
4	13.15±3.216	12.56±2.825	10.53±2.307	1.05	1.25	1.19
6	8.718±2.542	8.099±2.121	6.007±1.073	1.08	1.45	1.35
8	5.077±1.096	4.800±1.003	3.741±0.408	1.06	1.36	1.28
10	4.075±0.878	3.852±0.856	3.337±0.574	1.06	1.22	1.15
12	3.143±0.779	3.048±0.559	2.728±0.630	1.03	1.15	1.12
16	2.122±0.553	1.997±0.530	1.756±0.463	1.06	1.21	1.14
24	1.121±0.328	1.010±0.344	0.946±0.297	1.11	1.18	1.07
36	0.283±0.141	0.253±0.155	0.257±0.123	1.12	1.10	0.98
Parameters						
AUC_{0-t} (μg/mLxh)	113.9±16.30	112.4±19.34	120.1±20.56	1.01	0.95	0.94
AUC_{0-inf} (μg/mLxh)	116.9±17.91	115.4±20.28	123.4±20.81	1.01	0.95	0.93
C_{max} (μg/mL)	15.38±3.60	15.62±2.85	25.24±7.69	0.99	0.61	0.62
T_{max} (h)	3.564±1.46	2.666±0.89	1.501±0.92	1.34	2.37	1.78
Half-life (h)	6.864±1.17	6.637±1.25	7.063±0.83	1.03	0.97	0.94
Rate constant (h^{-1})	0.1036±0.02	0.108±0.02	0.099±0.01	0.96	1.04	1.08

Table 7

Etodolac Plasma Concentrations in the Food Study (N=13)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test-fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
AUC_{0-t} (μg/mLxh)	113.4±2.606	112.5±2.637	118.8±2.62	1.01	0.95	0.95
AUC_{0-inf} (μg/mLxh)	116.4±2.716	115.5±2.748	122.2±2.73	1.01	0.95	0.94
C_{max} (μg/mL)	14.99±1.264	15.39±1.278	24.80±1.27	0.97	0.60	0.62
T_{max} (h)	3.560±0.339	2.646±0.344	1.457±0.34	1.35	2.44	1.82
$LNAUC_{0-t}$ (Antiln)	4.721±0.022 (112.3)	4.710±0.022 (111.1)	4.763±0.022 (117.1)	1.01	0.96	0.95
$LNAUC_{0-inf}$ (Antiln)	4.746±0.022 (115.1)	4.736±0.022 (114.0)	4.792±0.022 (120.5)	1.01	0.96	0.95
LNC_{max} (Antiln)	2.684±0.064 (14.65)	2.724±0.064 (15.25)	3.150±0.064 (23.35)	0.96	0.63	0.65

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Capsules
Dose Strength: 200 mg, 300 mg
ANDA No.: 74840
Firm: Geneva Pharmaceuticals, Inc.
Submission Date: November 1, 1996
File Name: 74840SDW.N96

I. Conditions for Dissolution Testing: FDA method

USP XXII Basket: X Paddle: RPM:100
No. Units Tested: 12
Medium: 0.05 M pH 7.5 Phosphate Buffer Volume: 1000 mL
Specifications: NLT (Q) in 20 minutes
Reference Drug: Lodine® Capsules (Wyeth-Ayerst)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6496019 Strength(mg) 200			Reference Product Lot # 3940627 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
5	43		24.0	54		19.6
10	80		12.6	98		2.9
15	95		4.4	99		1.2
20	97		1.1	99		1.2
30	97		1.3	99		1.3

Sampling Times (Minutes)	Test Product Lot #6496016 Strength(mg) 300			Reference Product Lot # 3941207 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
5	21		25.2	24		35.8
10	67		26.0	57		23.2
15	92		11.0	91		10.7
20	101		2.2	101		4.6
30	102		1.9	103		0.8

Fasting Study

Figure 1: Mean Etodolac Plasma Levels

#005 – 32 – 11010

N = 23

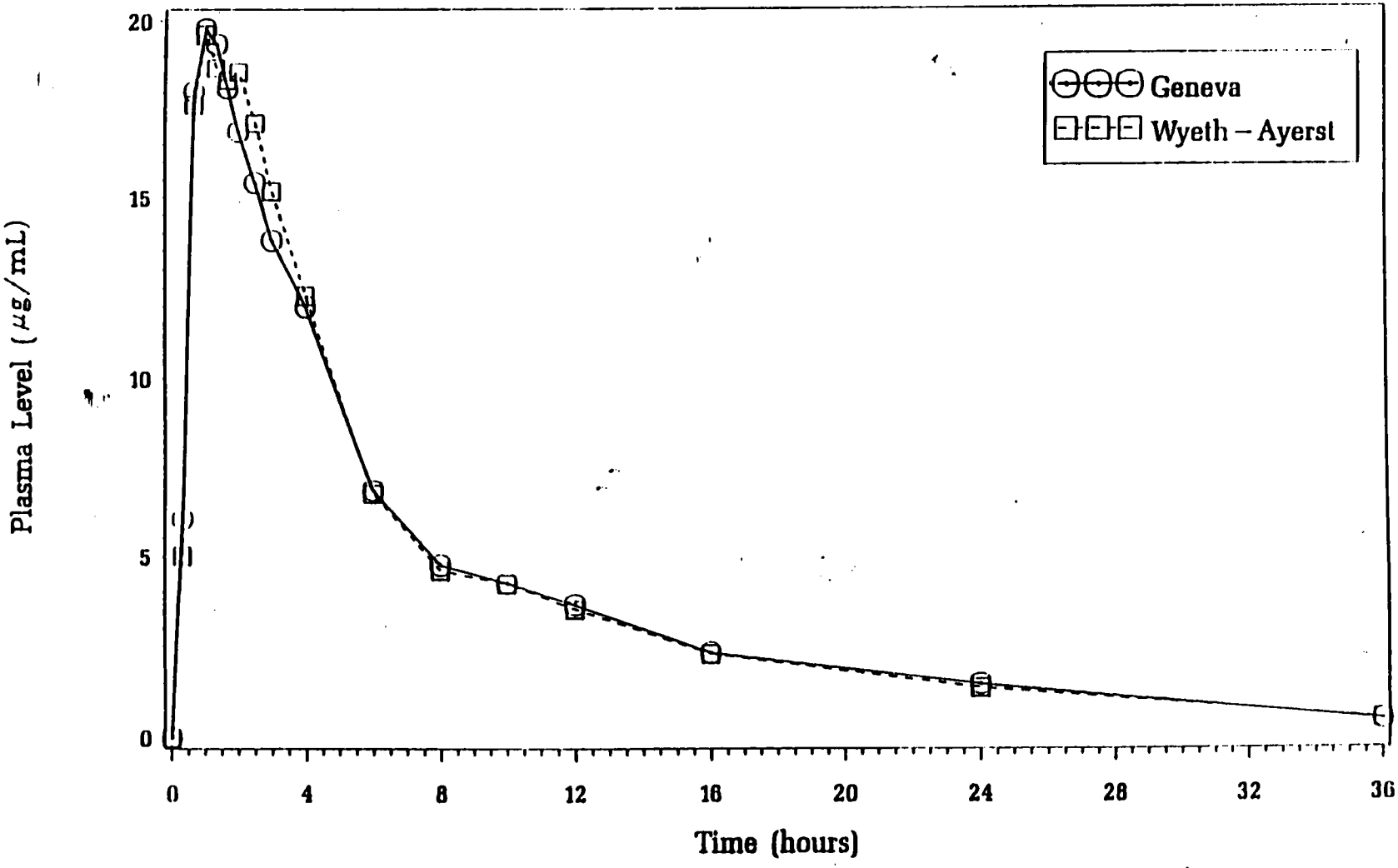


Figure 1

Figure 1: Mean Etodolac Plasma Levels

#005 – 33 – 11011

N = 13

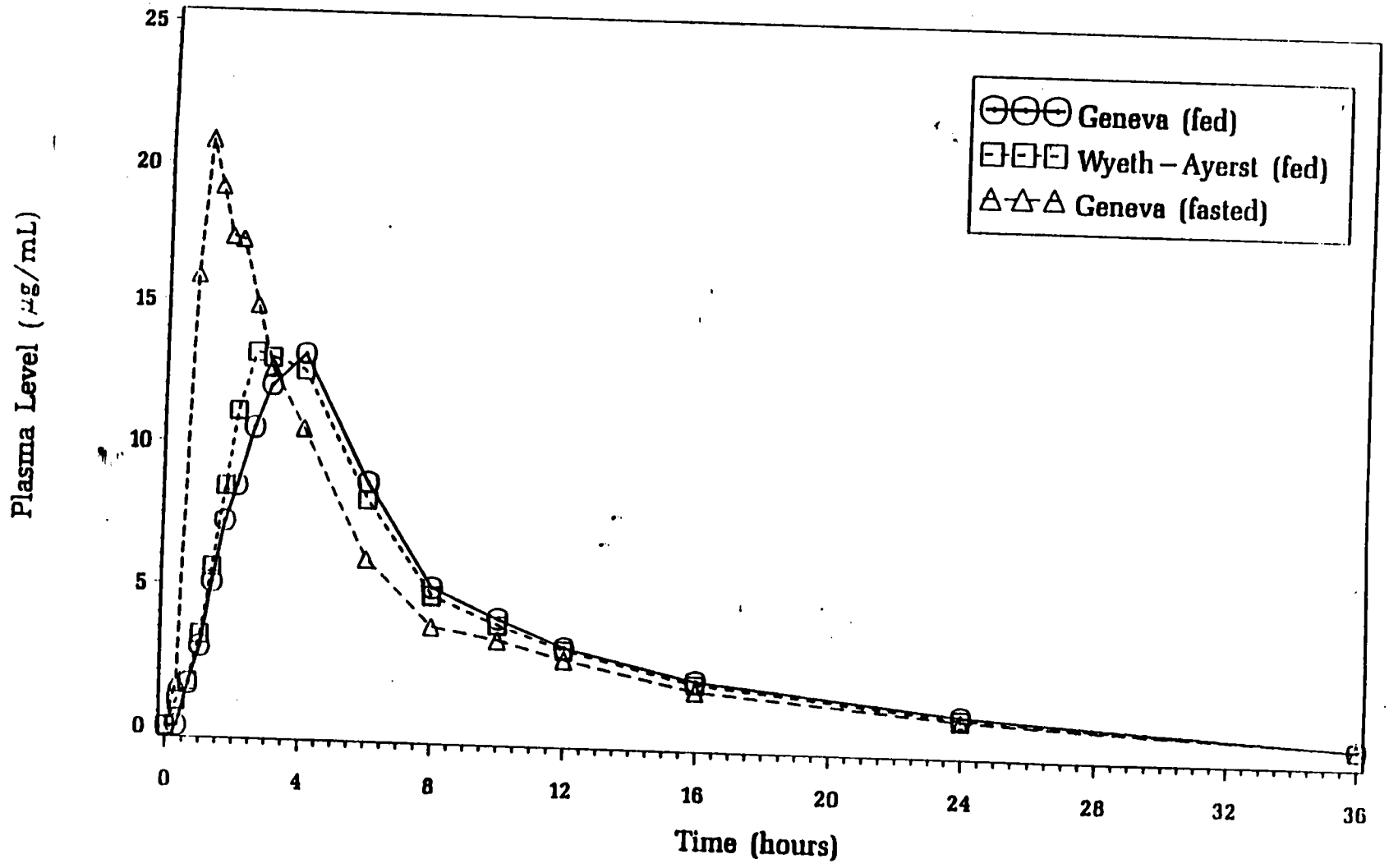


Figure 2.